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DOCUMENT-IDENTIFIER: US 5288502 A
TITLE: Preparation and uses of multi-phase microspheres

Abstract Paragraph Left (1):
Multi-phase polymeric microspheres containing a molecular compound dispersed in a polymeric matrix are described. Methods for preparing the multi-phase microspheres are also described, which includes a multiple emulsion solvent evaporation technique. Drug loading efficiencies between 80 to 100% were achieved using the described methods. Particular ratios of the W/O emulsion to polymer, and concentration of surfactant and dispersion media (mineral oil) provide highly efficient multi-phase microspheres. In particular embodiments, the multi-phase microspheres feature a high loading efficiency of water-soluble drugs, and also eliminates partitioning of the water soluble agent into the polymer acetonitrile (solvent) phase, thus preventing low encapsulation efficiency. The described multi-phase microspheres possess efficient drug loading, release properties, and drug stability, and also provide a vehicle for long term therapeutic release of a biologically active molecule for therapeutically effective periods of time. Molecular compounds which may be incorporated within the multi-phase microspheres include both water-soluble and water-insoluble drugs, proteins (e.g. TNF), peptides, and chemicals. The molecular compound is protected within an oily droplet, and contact with polymer, surfactant, organic solvents, and other potentially denaturing agents is prevented.

Brief Summary Paragraph Right (9):
Some of the inventors' prior work.sup.1 addresses the low efficiency of drug loading due to solubility problems by adjusting the pH of the aqueous phase in the microencapsulation procedure. Adjusting the pH of the aqueous phase was shown to maximize loading efficiency of the particular water-soluble molecule, quinidine sulfate, in PLA microspheres, using a conventional O/W emulsion system in the solvent evaporation process. One of the inventors had found that by increasing the pH of the water soluble molecular compound solution, the solubility of the water soluble molecular compound will increase in the solution. Thus, the water soluble molecular compound is prevented/inhibited from diffusing from the microcapsule into the external aqueous phase.

Brief Summary Paragraph Right (10):
Anhydrous emulsion systems have also been described in the preparation of microcapsules. For example, a phenobarbitone microencapsulation system was developed by Jalil and Nixon (1989).sup.18 using poly(1-lactic acid). Acetonitrile was used as the solvent ("W"-phase) for the poly(1-lactic acid) and the drug, and light mineral oil was used as the continuous dispersion medium (O-phase). However, in these microspheres, drug particles were dispersed in direct contact with the polymer matrix (conventional "matrix-type" system).

Brief Summary Paragraph Right (11):
Direct contact of drug particles with a polymer matrix has been observed to contribute to degradation of a protein,.sup.7 perhaps by monomer and diner residues present in the polymer (inventors' unpublished observations). Polymeric degradation would also result in such "matrix" systems upon incorporation of proteins or enzymes in such a system, as direct contact with the polymer is again not prevented.

Brief Summary Paragraph Right (12):
Most of the microspheres described in the literature belong to the class of "matrix-type" drug delivery capsules, in which the "foreign" (i.e. drug) particles are dispersed homogeneously in direct contact with the polymer. These processes also

frequently involve direct contact between the drug and a polymer solvent, such as acetonitrile or methylene chloride. In these systems, direct contact between the particular biologically active molecule and the polymer, the polymer solvent or with enzymes in the biological system promote degradation of the intended pharmaceutical. Specifically, previous workers have shown that the monomer and dimer residues in the polymer may degrade the protein, and other workers have shown that proteins.sup.7,32 and enzymes.sup.33 in direct contact with the polymer will result in polymeric degradation over time.

Brief Summary Paragraph Right (19):
Molecular compounds which are not stable in an aqueous solution may also be employed with the described multi-phase microspheres. For molecular compounds which are not particularly stable in water (e.g., subject to denaturation), the multi-phase microspheres of the present invention may be prepared by drying the final microspheres under a vacuum to remove any water which may be present in the microemulsion of the multi-phase microsphere.

Brief Summary Paragraph Right (21):
In all of the delivery systems described, the molecular compound is protected against continued denaturation from any included water. Alternatively, the microemulsion of the multi-phase microspheres of the present invention, containing a molecular compound which is unstable in water, may be prepared by first lyophilizing a preparation of the molecular compound in water and oil. The lyophilization will act to remove or decrease the water content of the preparation, thus preserving the stability of the molecular compound. The lyophilized form of the preparation thus takes on a powder form which may then be emulsified in a solution of a polymer and polymer solvent in a "dispersion" oil medium.

Brief Summary Paragraph Right (22):
For purposes of describing the subject matter of the present invention, the term, "multi-phase" relates to a modified matrix type microsphere wherein the molecular compound is not in direct contact with the polymer , while the term "conventional" relates to a matrix type of microsphere structure wherein the drug is dissolved or dispersed throughout the polymer matrix the drug being in direct contact with the polymer.

Brief Summary Paragraph Right (24):
In one particularly preferred aspect of the present invention, a microemulsion of a fixed oil and an aqueous solution of a water-soluble molecular compound, such as a protein, peptide or other water-soluble chemical if prepared. This emulsion is of the "water-in-oil" type (oil as the continuous phase) as opposed to an "oil-in-water" system (water as the continuous phase). The term "continuous phase" as used in the description of the present invention is the external phase, as compared to the "dispersed phase", which is the internal phase.

Brief Summary Paragraph Right (25):
The protein, peptide, chemical or other drug either after lyophilization of the molecular compound in a fixed oil mixture (in the case of a protein, peptide or drug denatured in the presence of water) or as a microemulsion prepared from the molecular compound in an aqueous phase in water (in the case of a protein, peptide or drug which is not denatured in the presence of water), is incorporated as part of the multi-phase microsphere of the present invention. The "external" oil phase of the microsphere includes an oil, such as mineral oil, which is incompatible with the particular solvent of a polymer-insolvent preparation.

Brief Summary Paragraph Right (26):
As the molecular compound of the present invention is effectively "trapped" within multiple tiny oil droplet reservoirs throughout the polymer matrix, the incorporated molecular compound does not partition into the polymer-insolvent outer phase during formulation, or into the polymer matrix of the hardened solvent evaporated multi-phase microsphere. Aluminum monostearate also helps to increase the viscosity of the fixed oil in which the molecular compound is effectively held, thus further preventing the molecular compound from diffusing out of the microsphere.

Brief Summary Paragraph Right (27):
A multiple emulsion technique with organic solvents to form microcapsules has been described generally in the past. However, none of the prior reported systems describe or suggest either a system wherein a water-insoluble molecular compound in a fixed oil, or a microemulsion of an aqueous solution of a water soluble protein or drug in

a fixed oil, is prepared and subsequently formulated in combination with a polymer-insolvent solution and dispersion (oil) medium. The present inventors describe for the first time molecular compound-in-oil preparation (mixture or microemulsion) as part of a multi-phase microsphere system. This unique design prevents contact of the molecular compound with potentially degrading substances, such as the polymer. The novel approach of lyophilizing a microemulsion of a particular water-denatured or unstable molecular compound and water in a fixed oil and mixing the lyophilized product with a solution of polymer and solvent in a dispersion oil broadens the applicability of the present invention for use with virtually any compound.

Brief Summary Paragraph Right (29):
In one particular embodiment of the present invention, a delivery system for a molecular compound comprising a multi-phase microsphere which includes a molecular compound contained within a fixed oil as part of a polymeric matrix is provided. The tern "molecular compound" as used in the description of the present invention includes peptides, proteins as well as other biocompatible and/or potentially bioactive/pharmacologically active molecules. Potentially useful molecular compounds which may be formulated in the disclosed multi-phase microspheres of the present invention include a variety of compounds known as "drugs" and other biocompatible macro- and micromolecules.

Brief Summary Paragraph Right (30):
Those compounds which are substantially or only partially soluble in water may also be used in conjunction with the disclosed multi-phase microsphere system upon enhancing the water solubility of the particular compound through adjustment of pH of the agent/compound in a water solution etc. before preparation of the aqueous solution of the water soluble agent/compound in oil to form a "microemulsion". Alternatively, molecular compounds which are unstable or exhibit minimal stability due to dehydration or denaturation upon exposure to water may be formulated as described with an additional step being included wherein the final multi-phase microspheres are dried under vacuum to remove any water from the microspheres. A second option of preparing a water/oil microemulsion of the drug and oil, as already described, with the microemulsion being lyophilized to remove or decrease the water content exists to preserve stability. Such a system would result in finely dispersed particles in the oil phase prior to the encapsulation process. The lyophilized powder which results may then be emulsified in a polymer and solvent and a dispersion oil medium.

Brief Summary Paragraph Right (31):
By way of example, molecular compounds which may be used in conjunction with the present invention included tumor-necrosis factor (TNF-.alpha. and .beta.), chlorpheniramine maleate (CPM), diphenhydramine hydrochloride (DPH), promazine hydrochloride (PMZ), and procainamide hydrochloride (PRC). Other pharmacologically active substances which may be prepared as a "microemulsion" of the present system, upon slight adjustment of pH, include the interferons (IFN-.alpha., .beta., .gamma.) macrophage activating factor (MAF), the interleukins (IL-1,2,3,4,5,6), colony stimulating factor (CSF), tumor degenerating factor (TDF), epidermal growth factor (EGF), erythropoietin (EPO), tissue plasminogen activator (TPA), insulin, urokinase, luteinizing hormone releasing hormone (LHRH), monoclonal antibodies, superoxide dismutase (SOD), the P-450 enzymes, bovine serum albumin (BSA), and oxytocin. Other water soluble molecular compounds which may be used in conjunction with the described method for preparing multi-phase microspheres include the steroids and atriopeptin III.

Brief Summary Paragraph Right (33):
Most preferably, the multi-phase microspheres of the present invention are about 150 microns (.mu.) in size. Even more preferably, the microspheres are between 50.mu. and 100.mu. in size. However, the microspheres of the present invention may be formulated to achieve virtually any size less than 150.mu. by adjustment of agitation rates, viscosity of the emulsion (i.e., lowering the viscosity of the oil), increasing the temperature used during formulation etc., sufficient to decrease particle size and prevent separation of the "microemulsion" particles from the polymer-insolvent mixture during formulation.

Brief Summary Paragraph Right (35):
The microemulsions (i.e., drug/protein solution-in-oil emulsion) described as part of the inventive multi-phase microspheres may be prepared with any variety of fixed oils. By way of example, such fixed oils include safflower, soybean, peanut, cotton

seed, sesame, or cod liver oil. Soybean, sesame, and safflower oil are most preferred in the preparation of the described "microemulsion". Oils used clinically in intravenous fat emulsions include the soybean and safflower oils.

Brief Summary Paragraph Right (36):
Mineral oil is most preferably used as part of the "dispersion" medium in the invention. The microemulsion, lyophilized molecular compound product or anhydrous molecular compound in fixed oil preparation is combined with a polymer/solvent in such a mineral oil dispersion medium to form the multiple emulsion of the invention. However, any oil may be used in the "dispersion" medium which is incompatible with the particular solvent used to dissolve the polymer.

Brief Summary Paragraph Right (37):
The present inventors have found that, provided the protein is stable in water, the formation of a microemulsion of the aqueous water-soluble protein molecular compound solution in oil, will stabilize the protein by preventing contact of the protein molecule directly with the polymer, the organic solvents, if any used, and any surfactants used to prepare the microspheres. Thus, the delivery system of the present invention includes an aqueous molecular compound solution-in-oil emulsion of the water soluble molecular compound which comprises numerous tiny oily reservoirs within the polymer matrix of the multi-phase microsphere. The water-soluble molecular compound thereby remains essentially isolated from all potentially degrading substances.

Brief Summary Paragraph Right (38):
The multi-phase microspheres of the delivery system comprise water soluble molecular compounds such as water-soluble proteins, peptides or drugs. Most preferably, the water-soluble molecular compound of the described delivery system includes CPM. In a most particularly preferred embodiment of the described delivery system, the molecular compound tumor-necrosis factor in water is prepared in the fixed oil, soybean oil, and the mixture lyophilized to a powder. The microemulsion of TNF in water with oil is lyophilized to remove essentially all of the water before dispersion of the microemulsion in the polymer solution (polymer plus polymer solvent), the mixture of which is then combined in a "dispersion" oil.

Brief Summary Paragraph Right (40):
This important observation highlights one particular advantage of the present systems over those proposed in the literature, in that a constant and fixed rate of delivery of a molecular compound is provided without sacrificing high drug loading efficiency in the microsphere. Other systems must be modified in order to achieve any particular rate of drug delivery, and currently do not provide for extended and slow drug release over therapeutically useful periods of time. The constant and slow rate of drug delivery may be attributable to the design of the multi-phase microspheres, which require that the molecular compound first traverse the water-oil barrier, and the polymer barrier of the polymer matrix, before the molecular compound/drug may diffuse out of the microsphere into the surrounding media or system (e.g., the system of an animal). Highly controlled and constant drug release is accomplished, along with the added advantage of greater than 80% drug loading efficiencies of these agents.

Brief Summary Paragraph Right (41):
Another aspect of the present invention includes a method for providing sustained release of a molecular compound (most preferably, water soluble molecular compounds) in an animal. One particularly preferred embodiment of this method comprises preparing a formulation comprising polymeric multi-phase microspheres containing a microemulsion of the water soluble molecular compound in a fixed oil and administering an amount of the formulation effective to provide sustained release of the water-soluble molecular compound in the animal for a prescribed period of time.

Brief Summary Paragraph Right (43):
In a most preferred aspect of the invention, the method includes a water-soluble molecular compound which is active as a therapeutic agent. A microemulsion of an aqueous solution of the water soluble molecular compound in a fixed oil is prepared and then mixed with a polymer solution and dispersion oil medium. No direct contact of organic solvent and the water soluble molecular compound therefor occurs.

Brief Summary Paragraph Right (46):
In still another embodiment of the present invention, a method for preparing multi-phase microspheres is provided. Most preferably, the claimed method for

preparing multi-phase microspheres containing a molecular compound comprises preparing a solution of the molecular compound (in water) with a fixed oil to form a microemulsion, mixing a biocompatible polymer and a polymer solvent together to form a polymer solution, dispersing the microemulsion into the polymer solution to form a W/O/"O" emulsion, mixing the W/O/"0" emulsion together in a dispersion oil which is incompatible with the polymer solvent to form a multiple emulsion, agitating and removing the solvent from the multiple emulsion to form hardened microspheres and washing and drying the hardened microspheres to form multi-phase microspheres containing the molecular compound. So prepared, the described -multi-phase microspheres are suitable for use as a long acting drug delivery device for virtually any protein, peptide, chemical or therapeutic agent. Where the particular molecular compound is unstable in water, the microemulsion may first be lyophilized to remove water and enhance the stability of the molecular compound before mixture with the polymer, polymer solvent and "dispersion" (oil) medium.

Brief Summary Paragraph Right (47):
Most preferably, the invention provides a method for preparing a multi-phase microsphere containing water-soluble molecular compounds. In this embodiment, an aqueous solution of the water soluble molecular compound is prepared. Where the molecular compound is stable in water, no lyophilization of the microemulsion is required before mixing same in a solution of polymer and solvent in a "dispersion" (oil) medium.

Brief Summary Paragraph Right (48):
Most preferably, the particular fixed oil of the microemulsion is soybean, safflower, cottonseed, peanut, sesame or cod liver oil. In addition, the microspheres may be most efficaciously prepared with the polymer solvent, acetonitrile. Again, the particular biodegradable polymer preferred for use in the preparation of the described microspheres is PLA or PLGA. Mineral oil would be used as a suitable oil of the "dispersion" medium where the polymer solvent is acetonitrile. Thus, the particular polymer-solvent mixture in a most particularly preferred embodiment of the claimed method is a PLA or PLGA/acetonitrile solution.

Brief Summary Paragraph Right (49):
As part of the claimed method, the solvent is removed from the W/O/"O" emulsion by the process of evaporation under atmospheric pressure, wherein the microemulsion is subject to constant agitation (i.e., stirring) in the dispersion (i.e., mineral oil) medium. The multi-phase microspheres produced according to the described method are most preferably about 150 microns (.mu.) in size. Even more preferably, the multi-phase microspheres are to be prepared so as to be between 100-200.mu. in size. Most preferably, the multi-phase microspheres may be prepared so as to attain a size of between about 50 microns and about 100 microns by slight modification of the speed or agitation and of the viscosity of the microemulsion/polymer solution system, employing other surfactants, modifying the dilutions of polymer solution employed, and/or increasing the temperature employed during formulation.

Brief Summary Paragraph Right (50):
In certain preferred embodiments of the described method, the water-soluble molecular compound is a water-soluble protein, peptide, chemical, dye or drug. Examples include brilliant blue, CPM, DPH, PMZ or PRC. Even more preferably, the aqueous phase described in conjunction with the preparation of the multi-phase microspheres includes Tween 80 at about 4% W/W, (or about 1% W/W of the microemulsion). In addition, the oil phase as described in the present methods most preferably includes Span 80, at a concentration of about 5% W/W (or 4% W/W in the W/O emulsion.

Brief Summary Paragraph Right (51):
In an even more particularly preferred embodiment of the method for preparing multi-phase microspheres containing a water-soluble molecular compound, the method comprises, preparing a first mixture of a water-soluble molecular compound in water, gelatin and Tween 80 to form an aqueous phase, preparing a second mixture of an amount of aluminum stearate (particularly, aluminum monostearate) and a volume of a fixed oil to provide a 2% aluminum stearate and about 5% (4% in the W/O emulsion) W/W of Span 80 oil phase, combining the first mixture with the second mixture to form a coarse W/O emulsion, processing the coarse W/O emulsion into a fine W/O microemulsion, preparing a third mixture of a biodegradable polymer and a polymer solvent, combining a quantity of the fine W/O microemulsion with the third mixture to form a W/O/"O" emulsion, preparing a fourth mixture of an oil incompatible A, with the polymer solvent and an amount of Span 80, pouring the W/O/"O" into the fourth mixture to form a multiple emulsion, agitating and evaporating the solvent from the

multiple emulsion to form hardened microspheres, separating the hardened microspheres from the mixture, and washing and drying the hardened microspheres to form multi-phase microspheres containing a water-soluble molecular compound. Most preferably, coarse W/O emulsion is processed to form a fine w/o emulsion by homogenizing the coarse W/O emulsion.

Brief Summary Paragraph Right (54):
The amount of the W/O emulsion dispersion inside the microspheres has also been observed by the present inventors to affect the loading efficiency of a particular biologically active agent into the microsphere preparation. Thus, the inventors have defined most preferred ranges of the quantity of the W/O emulsion which is to be included within those W/O/"O" emulsions in the current process. Thus, in a most particularly preferred embodiment of the claimed process, the quantity of the fine W/O emulsion (microemulsion) is to be between about 0.25 to 1.0 grams by weight per 1 gram of the polymer contained in the W/O/"O" emulsion.

Brief Summary Paragraph Right (57):
Where TNF is the molecular compound incorporated, controlled and constant drug release may be achieved for about 1 month. This time period will depend upon the molecular weight of the polymer used, the site of administration of the multi-phase microspheres, the polymer/drug ratio, the type and rate of degradation of the polymer (PLA>PLGA) used, the particle size of the "microemulsion," and other factors known to those in the art. It is hypothesized that the described multi-phase microspheres may be so formulated so as to highly controlled molecular compound release for up to 1 year in vivo.

Detailed Description Paragraph Right (1):
Novel multi-phase microspheres containing a molecular compound solution-in-oil microemulsion comprise the highly stable and slow releasing multi-phase microspheres of the present invention. The unique water-in-oil microemulsions are employed by the inventors in a multiple emulsion technique in the preparation a hybrid microsphere, defined as multi-phase microspheres. These multi-phase microspheres include numerous, tiny microemulsions in the form of oily droplets dispersed throughout a biodegradable polymer matrix. This technique innovatively provides for the elimination of contact between the polymer and the molecular compound, as well as enhancing the slow release characteristic of the compound from the microsphere.

Detailed Description Paragraph Right (2):
The elegant design of the compositions (i.e. multi-phase microspheres) and methods employing the compositions disclosed herein circumvent technical problems associated with microspheres and microcapsules described in the art, as well as those technical difficulties associated with providing efficient incorporation of a water soluble component in a drug delivery system. For example, the slow release action of the presently disclosed multi-phase microspheres make possible the design of in vivo treatment regimens which are effective over therapeutically valuable and/or necessary treatment periods. The present methods also eliminate the necessity of multiple injections and/or administration of the particular pharmaceutical. In addition, the unique "microemulsion" design included in the claimed multi-phase microspheres provides for high water soluble molecule loading efficiency without loss of slow and constant control of drug release, as compared to the content-dependent rate of drug delivery observed in conventional microsphere systems.

Detailed Description Paragraph Right (4):
Multiple emulsion systems with organic solvents have been described with some limited degree of success..sup.21 However, because a "microemulsion" of an aqueous solution of the drug in an oil, or of a drug in an oil (in the case of water-insoluble molecular compounds) is not employed as part of the preparation, the protein or enzyme is left in direct contact with the polymeric materials employed. Thus, the molecular compounds of such systems would be subject to denaturation/degradation through polymer contact, contact with a surfactant, organic solvent residuals and contact with organic solvents (e.g. acetonitrile). The potential for this type of degradation is eliminated through use of the disclosed methods, thus making microsphere delivery of potent and costly synthetic proteins and peptides a commercially feasible option.

Detailed Description Paragraph Right (5):
The presently described compositions and methods may be used with both water soluble molecular compounds and molecular compounds which are unstable in aqueous solutions. Denaturation of molecular compounds which are unstable in water may be prevented by

either first lyophilizing the microemulsion of the aqueous solution of the molecular compound in oil before the "dispersion" thereof in a solution of polymer and solvent and a dispersion oil, or by simply drying the final microspheres under a vacuum to remove water from the microspheres. Alternatively, the drug may first be dispersed within a fixed oil containing aluminum monostearate, and the drug-oil mixture combined with a polymer plus polymer solvent solution and a "dispersion" oil.

Detailed Description Paragraph Right (10):
The present example is provided to demonstrate one particularly preferred method by which the multi-phase microspheres of the present invention may be prepared with virtually any molecular compound. The multi-phase microspheres prepared in the present example were found to have a particle size of between about 150.mu. to 300.mu.. However, particles of smaller size (e.g., between 50.mu. to 100.mu., less than 150.mu.) may be obtained through modifying the presently described system as outlined in Prophetic Example 7.

Detailed Description Paragraph Right (11):
Molecular compounds that are soluble and stable in water (e.g. CPM, PMZ, DPH, PRC) may be prepared as an aqueous solution, which is then dispersed in an oil to form a microemulsion. Molecular compounds which are unstable (subject to denaturation in a water mixture with an organic solvent) (e.g., TNF), the final microspheres may be dried under vacuum to remove the water from the microspheres. Alternatively, a water/oil microemulsion of the drug may be prepared and the microemulsion lyophilized to remove or decrease the water content prior to emulsification in the dispersion oil and acetonitrile-polymer solution. This system would result in finely dispersed particles of the drug in the oil phase prior to the encapsulation process.

Detailed Description Paragraph Right (13):
The multi-phase microspheres were prepared by a multi-phase solvent evaporation process. The three-step emulsification process is described in FIG. 1. The preparation of the W/O emulsion (aqueous solution of a water-soluble molecular compound in a fixed oil (e.g., soybean oil or safflower oil)) constitutes step 1. This results in a unique "microemulsion" of the oil and the compound contained within a number of fine droplets.

Detailed Description Paragraph Right (15):
More specifically, the soybean oil in step 1 (FIG. 1) was heated to 140.degree. C/ to dissolve the aluminum stearate (2% w/w), after which the oil phase was cooled to 40.degree. C. The aqueous phase (25 ml) containing the water-soluble molecular compound, in this case brilliant blue or CPM, and gelatin (1% w/w), and Tween 80 (4% w/w) was poured into the oil phase (75 ml) containing Span 80 (4% w/w) and agitated in order to obtain a coarse W/O emulsion. The W/O emulsion was then homogenized with a microfluidizer (model M-110T) until a fine microemulsion was obtained.

Detailed Description Paragraph Right (16):
In step 2, the polymer and polymer solvent solution was added. PLA or PLGA are the preferred biodegradable polymers. Each of these polymers (about 3 grams) were first dissolved in a volume of acetonitrile (about 4 grams, Fischer Scientific Co.). The W/O microemulsion (drug gelatin, Tween 80, Span 80, soybean oil, aluminum stearate) was poured int this polymer-acetonitrile solution and dispersed to form a W/O/"O" emulsion (multiple emulsion).

Detailed Description Paragraph Right (19):
Span 80 and Tween 80 were used as emulsifying agents to make a water (aqueous water soluble molecular compound solution) in soybean oil (W/O) emulsion. This W/O emulsion was found to be unstable in the PLA or PLGA-acetonitrile solutions (step 2), and the aqueous phase of the emulsion was readily released into the acetonitrile solution due to phase inversion. The addition of aluminum monostearate to soybean oil was effective in preventing phase inversion with the W/O emulsion by increasing the viscosity and plasticity of the soybean oil. Aluminum monostearate has been previously used as a hardening agent for oils in non-aqueous penicillin G suspensions for injections. The levels of Span 80 and Tween 80 were optimized to decrease the size of the aqueous phase in the W/O emulsions prepared by homogenization.

Detailed Description Paragraph Right (28):
The loading efficiency of TNF into multi-phase and conventional (i.e., matrix) microspheres was measured and compared. The data obtained is presented in Table 2.

Detailed Description Paragraph Right (29):

The TNF loading efficiency in batch 1 of the multi-phase microspheres was 89.9%, while TNF loading efficiency for batch-2 multi-phase microspheres was 88.9%. The mean TNF loading efficiency into multi-phase microspheres of both batch 1 and batch 2 preparations was 89.4%. The TNF loading efficiency observed in conventional (matrix-type) microspheres, batch 1 was 69.8%. TNF loading efficiency in batch 2 conventional (matrix) microspheres was 62.5%. The average TNF loading efficiency into conventional (matrix) microspheres was 66.2%. These data demonstrate a significant enhancement in TNF loading efficiency using multi-phase microspheres, as compared to conventional matrix type microsphere systems.

Detailed Description Paragraph Right (34):
At low (below about 22.2% for PLA, below about 16.7% for PLGA) concentrations of PLA or PLGA in acetonitrile, it was difficult to disperse the W/O emulsions (the microemulsion) into the polymer solution, and therefore multi-phase microspheres containing the W/O emulsions were not obtained.

Detailed Description Paragraph Right (35):
As the concentration of the polymers in acetonitrile increased to at least about 16% (the lowest limit being about 22.2% for PLA and about 16.7% for PLGA), dispersion of the W/O emulsion (microemulsion) droplets in the polymer-acetonitrile solution improved. This was attributed to a synergistic effect of the surface-protecting characteristics of the polymer, increased viscosity of the polymer/acetonitrile solution, and cancellation of the density difference between the W/O emulsion (microemulsion) and the acetonitrile medium by the addition of the polymer. At high polymer concentrations, the microspheres aggregated during the process of the solvent evaporation (FIG. 1, step 3). Relatively large and viscous polymer-acetonitrile solution droplets containing the W/O emulsions resulted in irregularly shaped unhardened masses. These masses were observed to cause adhesion to other masses and unhardened microsphere beads.

Detailed Description Paragraph Right (37):
Loading efficiencies of brilliant blue, DPH, PMZ, and PRC into the multi-phase microspheres were examined with various amounts of the W/O emulsions (microemulsion) dispersed in 3.25 g of PLGA-acetonitrile solution (30.8% w/w) containing 1.00 g of PLGA. The results in FIG. 12 depict the drug loading efficiencies versus the weight of the W/O emulsions when the multi-phase microspheres were prepared using light mineral oil (the "dispersion" medium) containing 0.25% of Span 80. The W/O emulsion weights ranging from 0.25 to 0.75 g gave relatively high loading efficiencies (.gtoreq.80%).

Detailed Description Paragraph Right (49):
Multi-phase microspheres of poly (d,l-lactic acid) (PLA) or poly (d,l-lactic co-glycolic acid) (PLGA) containing a water soluble molecular compound solution in oil (W/O) emulsion were prepared by the multiple emulsion solvent evaporation technique described in Example 1. Either CPM or brilliant blue was employed as the water-soluble molecule, to which was added gelatin (about 1% W/V in aqueous phase, Fisher Scientific Company), Tween 80 and distilled water. The fixed oil with which the water-soluble molecular compound was mixed was soybean oil. The soybean oil also included an amount of about 2.0% W/W aluminum monostearate to which about 4% w/w Span 80 was added in about 93.5% soybean oil. The above two -mixtures were combined and agitated to form a "microemulsion".

Detailed Description Paragraph Right (50):
The polymer/solvent mixture was then prepared, into which the "microemulsion" was poured and mixed together in a dispersion medium of mineral oil and Span 80. Acetonitrile was used as the polymer solvent. A mixture of light mineral oil and Span 80 was employed as the dispersion medium.

Detailed Description Paragraph Right (51):
The polymeric multi-phase microspheres contained oil-drug reservoirs throughout the polymer matrix, with the water-soluble drug being contained within an aqueous dispersed phase inside the oily droplet.

Detailed Description Paragraph Right (52):
Conventional PLGA microspheres containing either CPM or brilliant blue were prepared by an acetonitrile-in-oil (W/O) emulsion solvent evaporation technique substantially as described by Jalil and Nixon.sup.3,4. The CPM and the PLGA were dissolved in the acetonitrile ("W" phase). Similarly, a preparation of brilliant blue and PLGA were dissolved in acetonitrile. Light mineral oil was used as the evaporation (dispersion)

medium in both preparations (O phase). So formed, the resulting conventional CPM or brilliant blue containing microspheres were prepared to provide contact with the polymer matrix.

Detailed Description Paragraph Right (62):
A micrograph of the PLGA multi-phase microspheres containing brilliant blue, as observed by transmitted-light, is shown in FIG. 8-A. The dark areas in the microsphere beads are the W/O emulsions containing brilliant blue. Scattered fine particles seen in the polymer wall are brilliant blue particles that have leaked out of the W/O emulsions. Cavities were observed in the cross sections of the microspheres under reflected light conditions. These results demonstrate that the multi-phase microspheres belong to a class of hybrid matrix type drug delivery devices not before recognized. The distribution of the dye in the PLGA microspheres prepared by the conventional method is seen in FIG. 8-B.

Detailed Description Paragraph Right (77):
Lag time stages were observed in the release profiles of the conventional microspheres. This was attributed to the time required for water to penetrate into the polymer matrix and for sufficient polymer degradation to form aqueous channels through which the drug could diffuse out of the microspheres. During this lag time period, the erosion of the polymer wall of the conventional microspheres developed to form failures or cracks which were seen between the lamellas (FIG. 6-B). These lamellas were created by the polymer erosion along the discontinuous interfaces between the laminated PLGA precipitates which were hardened concentrically from the surface to the center of the beads. After 2 weeks, the porous sponge-like structures were observed in the polymer wall and the pores had developed toward the center of the beads. Some shallow portions beneath the surface of the beads had already eroded and evacuated. However, the surface portions of the beads remained almost intact even after 2 weeks (FIG. 9-A).

Detailed Description Paragraph Right (89):
Molecular weight of PLGA was determined by GPC in tetrahydrofuran using a set of three Ultrastyragel columns (Waters) with nominal pore size of 10.sup.3, 10.sup.2, and 10 nm, and a flow rate of 1 ml/min. The molecular weights were evaluated by elution volume against polystyrene standards (Polysciences, Inc.).

Detailed Description Paragraph Right (97):
The PLGA polymer degradation rates of the conventional and multi-phase microspheres were virtually the same when the microspheres contained either brilliant blue or CPM. Thus, the inclusion of a water soluble compound and the particular amount of same in the W/O emulsion (microemulsion) in the multi-phase microspheres did not affect the PLGA degradation. In addition, the water soluble molecular compounds contained within the microspheres did not appear to affect the degradation of the polymer.

Detailed Description Paragraph Right (100):
The PLGA multi-phase microspheres demonstrated a two-stage release property which was independent of the brilliant blue and CPM content and their physiochemical characteristics, while the release profiles of the conventional matrix type microspheres had lag time and were affected by the drug content and the brilliant blue.

Detailed Description Paragraph Right (101):
The present prophetic example is provided to describe methods whereby the particle size of the microspheres may be reduced so as to provide a preparation of small (i.e., less than 150.mu., preferably between about 50.infin. to about 100.mu.) multi-phase microspheres. The present example will also outline methods whereby particular water soluble or partially water soluble proteins and peptides may be incorporated into the described multi-phase microsphere system.

Detailed Description Paragraph Right (102):
Drugs such as decongestants, antihistamines, biological response modifiers (such as the interferons, interleukins, NAF (macrophage activating factor), SCF, TDF, EGF, EPO, TPA, ANP (arterial natriuretic peptide), etc.), antiviral agents (idoxuridine, amantadine, interferon, etc.), hemoproteins (P-450 enzymes, etc.), hormones (insulin, LHRH), enzymes (urokinase), may be prepared as part of a "microemulsion" in, for example, a volume of soybean oil, and then incorporated into the described multi-phase microsphere protocol outlined in Example 1 and FIG. 1.

Detailed Description Paragraph Right (104):

A slight adjustment of the pH of the aqueous phase (i.e., the protein inside the oil droplet) and/or stabilizing agent for drugs may be necessary in order to enhance the stability of the protein (i.e., the microemulsion) and/or the solubility of the protein as part of the multi-phase microsphere preparation may be needed. Such may be accomplished by, for example, using the acid, hydrochloric acid, citric acid or sodium phosphate mono-basic to adjust the pH of the aqueous solution to the desired pH. Buffers such as phosphate buffer, acetate buffer and citrate buffer may also be used to adjust pH. By way of example, agents which may be used as stabilizing agents include sugars (glucose, sucrose, fructose, lactose, mannose, mannitol, etc) and polysaccharides (glycogen, starch, CMC-NA (sodium carboxymethycellulose), HPC (hydroxypropyl cellulose), HPMC (hydroxypropyl methyl cellulose), HPMCP (hydroxypropyl methyl cellulose phthalate), etc.), amino acids, peptides (albumin, globulin, gelatin, collagen, etc.), mucopolysaccharides (chondroitin sulfate, dextran sulfate, etc.), mucopolysaccharides (chondroitin sulfate, dextran sulfate, heparin sodium, hyaluronic acid, etc.), pluronic, polyethyleneglycols, polyacrylates, PVP (poly vinyl pyrollidone), and PVA (poly vinyl acetate).

Detailed Description Paragraph Right (108):
The microemulsion so adjusted for pH to solubilize/stabilize the protein, will then be mixed with a polymer containing solvent, such as PLA in acetonitrile, and the multi-phase microspheres prepared substantially as described for the remainder of the procedure in FIG. 1.

Detailed Description Paragraph Right (109):
Multi-phase microspheres may be prepared with the particular family of proteins known as the interleukins, which include IL-1, 2, 3, 4, and 6. It may be necessary to adjust the pH of the aqueous phase contained in the W/O emulsion to the isoelectric point of the particular interleukin species. For example, the isoelectric point of the dominant species of interleukin 1 is between 6.8 to 7.3. The isoelectric point of the minor species of interleukin 1 is between 5.3 and 5.8. (see, the Merck Index, 11th Edition, p. 4895-4896). By adjustment of the W/O microemulsion or oily suspension of the interleukin, one may accomplish the desired stability and/or solubility of this particular agent in the system.

Detailed Description Paragraph Right (111):
The multi-phase microspheres prepared thus far have a size of about 150.mu.. Microspheres of smaller diameter may be prepared by increasing the temperature of the oil phase, provided the drug is stable in the emulsion. Higher agitation speeds will also be successful if that is coupled with a high concentration of polymer in the acetonitrile to prevent the loss of emulsion from the microsphere. In addition, a dry (lyophilized) emulsion system can be used for preparation of multi-phase microspheres instead of the W/O microemulsion. Where a stainless steel propeller device is employed to agitate the multiple emulsion, agitation speeds should be increased to, for example, 250, 400, 500 and 600 rpm to achieve small (<150.mu.) multi-phase microspheres.

Detailed Description Paragraph Center (26):
Proposed Methods for Reducing Multi-phase Microsphere Size to Between 50.mu.-100.mu.

Detailed Description Paragraph Type 0 (7):
Prophetic Example7--Proposed Methods for Preparing Multi-Phase Microspheres with Water-Soluble Peptides and Proteins and Multi-phase Microspheres of Less than 150.mu. Size.

Detailed Description Paragraph Table (2):
TABLE 2 _____ Comparison of TNF loading efficiency between multi- phase and conventional microspheres. Type of Particle Loading Weight microspheres Batch*1 size range efficiency Fraction parameter number D E % W _____ Multi-phase 1 100-250 .mu.m 78.5% 0.474 250-500 100.2 0.526 100-500 89.9*2 1.000 2 100-250 85.5 0.757 250-500 99.8 0.243 100-500 88.9*2 1.000 over all 100-250 82.0*3 0.616 mean of 250-500 100.3*3 0.384 1 and 2 100-500 89.4*3 1.000 Conventional 1 100-250 .mu.m 53.6% 0.478 250-500 70.6 0.522 100-500 69.8*2 1.000 2 100-250 68.7 0.594 250-500 71.6 0.405 100-500 62.5*2 1.000 over all 100-250 61.2*3 0.536 mean of 250-500 71.1*3 0.464 1 and 2 100-500 66.2*3 1.000 _____ *1 Solvent evaporation (step 3) was carried out at agitating speed at 400 rpm (batch1) and 500 rpm (batch2). *2 Loading efficiency (100-500 um) was calculated as follows: E %(100-500) ##STR1## *3 Loading efficiency (a-b .mu.m) was calculated as follows: ##STR2##

Current US Original Classification (1):
424/484

Current US Cross Reference Classification (1):
424/488

Current US Cross Reference Classification (2):
424/489

Current US Cross Reference Classification (3):
424/490

Current US Cross Reference Classification (4):
424/491

Other Reference Publication (1):
Alex et al. (1987) N. J. Microencapsulation, vol. 7, No. 3, 347-355 Encapsulation of Water Soluble Drugs by a Modified Solvent Evaporation Method. In: Effect of Process and Formulation Variable on Drug Entrapment.

CLAIMS:

1. A delivery system for a protein, peptide, or drug with biodegradable multi-phase microspheres, said microspheres comprising a protein, peptide, or drug contained within a fixed oil and an essentially water insoluble, biodegradable polymeric matrix comprised of polylactic acid or polylactic glycolic acid wherein the polymeric matrix surrounds the fixed oil of the microsphere and wherein the fixed oil contains the protein, peptide, or drug.

2. A delivery system for a water-soluble protein, peptide, or drug with biodegradable multi-phase microspheres, said microspheres comprising a microemulsion of a water soluble protein, peptide, or drug, a fixed oil and a biodegradable, essentially water insoluble polymeric matrix of polylactic acid or polylactic glycolic acid, said polymeric matrix surrounding the microemulsion of fixed oil and the protein, peptide, or molecular compound.

3. A delivery system for cytokines with biodegradable multi-phase microspheres, said microspheres comprising a cytokine contained within a fixed oil, and an essentially water insoluble, biodegradable polymeric matrix of polylactic acid or polylactic glycolic acid, wherein the polymeric matrix surrounds the fixed oil and wherein the fixed oil contains the cytokine.

4. A delivery system for tumor necrosis factor with biodegradable multi-phase microspheres said microspheres comprising a lyophilized microemulsion of an aqueous solution of tumor necrosis factor in a fixed oil, and an essentially water insoluble, biodegradable polymeric matrix of polylactic acid or polylactic glycolic acid, wherein the polymeric matrix surrounds said microemulsion of tumor necrosis factor and fixed oil.

6. The delivery system of claim 1, 2, 3 or 4 wherein the multi-phase microsphere is about 150.mu. in size.

7. The delivery system of claim 1, 2; 3 or 4 wherein the multi-phase microsphere is about between 50.mu. to 100.mu. in size.

9. The delivery system of claim 8 wherein the molecular compound is prepared as an aqueous solution together in a fixed oil to provide a microemulsion.

17. The delivery system of claim 4 or 6 wherein the microemulsion consists of lyophilized tumor necrosis factor in a fixed oil and the polymeric matrix is poly-lactic acid (PLGA).

19. A method for providing sustained release of a protein, peptide, or drug in an animal comprising:

preparing a formulation of microspheres, said microspheres containing the protein, peptide, or drug in a fixed oil, and a biodegradable essentially water insoluble polymeric matrix of polylactic acid or polylactic glycolic acid; and

administering an amount of the formulation effective to provide sustained release of the protein, peptide, or drug in the animal for a prescribed period of time, wherein the polymeric matrix surrounds the fixed oil and the fixed oil contains the protein, peptide, or drug.

25. The method of claim 19 wherein the protein, peptide, or drug is water-soluble and is prepared as an aqueous solution together in a fixed oil to provide a microemulsion and wherein the polymeric matrix surrounds the microemulsion.

29. A method for preparing multi-phase microspheres containing a protein, peptide, or dug comprising:

mixing an aqueous solution of the protein, peptide, or drug with a fixed oil to form a W/O microemulsion;

mixing polylactic acid or polylactic glycolic acid and a polymer solvent together to form a polymer solution;

dispersing the microemulsion into the polymer solution to form a W/O/"O" emulsion;

mixing the W/O/"O" emulsion together in a dispersion oil which is incompatible with the polymer solvent to form a multiple emulsion;

agitating and removing the solvent from the multiple emulsion to form hardened microspheres; and

washing and drying the hardened microspheres to form multi-phase microspheres containing the water-soluble protein, peptide, or drug.

30. The method of claim 29 wherein the fixed oil of the microemulsion is soybean, cottonseed, peanut, sesame cod liver oil or safflower oil.

35. The method of claim 29 wherein the microspheres are about 150.mu. in size.

36. The method of claim 29 wherein the microspheres are between about 50.mu. and about 100.mu. in size.

38. The method of claim 29 wherein the microemulsion comprises about 1% w/w Tween 80 of the microemulsion.

39. The method of claim 29 wherein the microemulsion comprises about 2% aluminum monostearate and about 5% W/W Span 80 of the microemulsion.

42. The method of claim 2 wherein the ratio of microemulsion to polymer is between about 0.25 to 1.0 grams to 1 by weight.

43. The method of claim 29 wherein the molecular compound is unstable in water, and wherein the microemulsion is lyophilized prior to dispersing the microemulsion into the polymer solution to form a W/O/"W" emulsion.

45. A method for preparing microspheres containing a water-soluble drug comprising:

preparing a first mixture of a water-soluble drug in water, gelatin and Tween 80 to form an aqueous phase;

preparing a second mixture of an amount of aluminum stearate and a volume of a fixed oil to produce a 2% w/w aluminum stearate and about 5% w/w Span 80 oil phase;

combining the first mixture with the second mixture to form a coarse W/O emulsion;

processing the coarse W/O emulsion into a fine W/O microemulsion;

preparing a third mixture of polylactic acid or polylactic glycolic acid and a solvent;

combining a quantity of the fine W/O microemulsion with the third mixture to form a W/O/"O" emulsion;

preparing a fourth mixture of an amount of Span 80 and an oil incompatible with the

polymer solvent;

pouring the W/O/"O" emulsion into the fourth mixture to form a multiple emulsion;

agitating and evaporating the polymer solvent from the multiple emulsion to form hardened microspheres;

separating the hardened microspheres from the mixture; and

washing and drying the hardened microspheres to form multi-phase microspheres containing a water-soluble drug.

54. A multi-phase microsphere for the delivery of a peptide, protein, or drug comprising a biodegradable essentially water insoluble polymeric matrix of polylactic acid or polylactic glycolic acid surrounding a protein, peptide, or drug contained within a fixed oil, said microsphere prepared by a process of:

preparing a first mixture of a water-soluble protein, peptide, or dug in water, gelatin and Tween 80 to form an aqueous base;

preparing a second mixture of an amount of aluminum stearate and a volume of a fixed oil to produce a 2% w/w aluminum stearate and about 5% w/w span 80 oil phase;

combining the first mixture with the second mixture to form a coarse W/O emulsion;

processing the coarse W/O emulsion into a fine W/O micro emulsion;

preparing a third mixture of a biodegradable essentially water-insoluble polymer polylactic acid of polylactic glycolic acid and a solvent;

combining a quantity of the fine W/O micro emulsion with the third mixture to form a W/O/"O" emulsion;

preparing a fourth mixture of an amount of span 80 and an oil incompatible with the polymer solvent;

pouring the W/O/"O" emulsion into the fourth mixture to form a multiple emulsion;

evaporating the solvent from the multiple emulsion to form hardened microspheres;

separating the hardened microspheres from the mixture; and

washing and drying the hardened microspheres to form multi-phase microspheres containing a water-soluble protein, peptide, or drug.

58. A biodegradable polymeric microsphere comprising an essentially water insoluble poly (d,l-lactic acid) or poly (d,l-lactic) co-glycolic acid polymeric matrix surrounding a protein-containing fixed oil droplet.

59. The biodegradable polymeric microsphere of claim 58 wherein the polymeric matrix is poly(d,l-lactic acid).

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Search Results - Record(s) 1 through 10 of 26 returned.

1. Document ID: US 6365189 B1

L4: Entry 1 of 26 File: USPT Apr 2, 2002

US-PAT-NO: 6365189
DOCUMENT-IDENTIFIER: US 6365189 B1

TITLE: Method of delivering and releasing a pheromone

DATE-ISSUED: April 2, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Quong; Douglas	London			CAX

US-CL-CURRENT: 424/489; 424/499, 424/500

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

2. Document ID: US 6309663 B1

L4: Entry 2 of 26 File: USPT Oct 30, 2001

US-PAT-NO: 6309663
DOCUMENT-IDENTIFIER: US 6309663 B1

TITLE: Triglyceride-free compositions and methods for enhanced absorption of hydrophilic therapeutic agents

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Patel; Mahesh V.	Salt Lake City	UT		
Chen; Feng-Jing	Salt Lake City	UT		

US-CL-CURRENT: 424/450; 424/435, 424/451, 424/455, 424/456, 424/463, 424/464, 424/489, 424/499, 424/502, 514/937, 514/938, 514/939, 514/940, 514/941, 514/942, 514/943, 514/975

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

3. Document ID: US 6309633 B1

L4: Entry 3 of 26 File: USPT Oct 30, 2001

US-PAT-NO: 6309633
DOCUMENT-IDENTIFIER: US 6309633 B1

TITLE: Amphiphilic drug-oligomer conjugates with hydroyzable lipophile components and methods for making and using the same

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ekwuribe; Nnochiri	Cary	NC		
Ramaswamy; Muthukumar	Cary	NC		
Rajagopalan; Jayanthi Sethuraman	Cary	NC		

US-CL-CURRENT: 424/85.1; 424/193.1, 424/194.1, 424/85.2, 424/85.4, 424/94.3, 435/188, 514/12, 514/2, 514/21, 514/3, 514/476, 514/506, 514/579, 514/613, 514/715, 514/8, 530/303, 530/345, 530/405, 530/406, 530/409, 530/410 , 530/411

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6291516 B1

L4: Entry 4 of 26 File: USPT Sep 18, 2001

US-PAT-NO: 6291516
DOCUMENT-IDENTIFIER: US 6291516 B1

TITLE: Regulators of the hedgehog pathway, compositions and uses related thereto

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dudek; Henryk	Wellesley	MA		
Ji; Benxiu	Sharon	MA		

US-CL-CURRENT: 514/455; 424/236.1, 424/240.1, 514/169, 514/173, 514/182, 514/222.5, 514/226.2, 514/236.2, 514/257, 514/275, 514/280, 514/311, 514/314, 514/317, 514/327, 514/331, 514/346, 514/347, 514/397, 514/415, 514/420, 514/424, 514/47, 514/470, 514/473, 514/478, 514/479, 514/523, 514/530, 514/535, 514/537, 514/538 , 514/573, 514/605, 514/617, 514/620, 514/642, 514/651, 514/652, 514/653, 514/863, 600/562

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☑ 5. Document ID: US 6248363 B1

L4: Entry 5 of 26 File: USPT Jun 19, 2001

US-PAT-NO: 6248363
DOCUMENT-IDENTIFIER: US 6248363 B1

TITLE: Solid carriers for improved delivery of active ingredients in pharmaceutical compositions

DATE-ISSUED: June 19, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Patel; Mahesh V.	Salt Lake City	UT		
Chen; Feng-Jing	Salt Lake City	UT		

US-CL-CURRENT: 424/497; 424/422, 424/427, 424/430, 424/433, 424/434, 424/435, 424/436, 424/441, 424/451, 424/457, 424/463, 424/464, 424/465, 424/466, 424/470, 424/474, 424/476, 424/482, 424/489, 424/490, 424/498, 514/772.3, 514/773, 514/779, 514/784, 514/785, 514/786

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 6. Document ID: US 6183774 B1

L4: Entry 6 of 26 File: USPT Feb 6, 2001

US-PAT-NO: 6183774
DOCUMENT-IDENTIFIER: US 6183774 B1

TITLE: Stabilizing vitamin A derivatives by encapsulation in lipid vesicles formed with alkylammonium fatty acid salts

DATE-ISSUED: February 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aust; Duncan T.	Ridge	NY		
Ross; Michael A.	Jericho	NY		
Wilmott; James M.	Shoreham	NY		
Hayward; James A.	Stony Brook	NY		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 424/401, 514/724, 514/725

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 7. Document ID: US 6183773 B1

L4: Entry 7 of 26 File: USPT Feb 6, 2001

US-PAT-NO: 6183773
DOCUMENT-IDENTIFIER: US 6183773 B1

TITLE: Targeting of sebaceous follicles as a treatment of sebaceous gland disorders

DATE-ISSUED: February 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anderson; Richard Rox	Lexington	MA		

US-CL-CURRENT: 424/450; 424/401, 424/70.1, 424/70.8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 8. Document ID: US 6147060 A

L4: Entry 8 of 26 File: USPT Nov 14, 2000

US-PAT-NO: 6147060
DOCUMENT-IDENTIFIER: US 6147060 A

TITLE: Treatment of carcinomas using squalamine in combination with other anti-cancer

agents

DATE-ISSUED: November 14, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zasloff; Michael	Merion Station	PA		
Williams; Jon	Robbinsville	NJ		

US-CL-CURRENT: 514/110; 424/649, 514/171, 514/34, 514/589

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☑ 9. Document ID: US 6103271 A

L4: Entry 9 of 26 File: USPT Aug 15, 2000

US-PAT-NO: 6103271
DOCUMENT-IDENTIFIER: US 6103271 A

TITLE: Microencapsulation and electrostatic processing method

DATE-ISSUED: August 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morrison; Dennis R.	Kemah	TX		
Mosier; Benjamin	Houston	TX		

US-CL-CURRENT: 424/490; 264/4.32, 264/4.33, 424/450, 424/489, 424/491, 424/497, 424/498, 427/213.3, 428/402.21, 428/402.24, 514/772.3, 514/773

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 10. Document ID: US 6099864 A

L4: Entry 10 of 26 File: USPT Aug 8, 2000

US-PAT-NO: 6099864
DOCUMENT-IDENTIFIER: US 6099864 A

TITLE: In situ activation of microcapsules

DATE-ISSUED: August 8, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morrison; Dennis R.	Kemah	TX		
Mosier; Benjamin	Houston	TX		

US-CL-CURRENT: 424/489; 264/4.1, 264/4.3, 264/4.32, 264/4.33, 424/423, 424/450, 428/402.2, 428/402.21, 514/951

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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